Remarks

Claims 44 and 52-56 are pending. Claims 43 and 46 have been cancelled. The Applicants have incorporated the subject matter of claim 46 into claim 44. Claim 52 has been amended to depend from claim 44 instead of now cancelled claim 43. Paragraph [0064] of the application has been amended to include material previously incorporated into the application by reference. Entry of these changes into the official file is respectfully requested.

Support for the amendments to claim 44 and paragraph [0064] can be found in Lu and Andrieu, 75 J. Virol. 8949 (2001) (hereinafter Lu), the entire disclosure of which is incorporated by reference into this application at page 34, and paragraph [0050] which states that patients received dendritic cells comprising "autologous HIV[.]" This application is based on the work disclosed in Lu which teaches at page 8950, consistent with the disclosure at paragraph [0064] on page 17 of the application, that autologous HIV "[v]iruses were isolated by coculture of phytohemagglutinin (Sigma, St. Louis, Mo.)-stimulated HIV-negative donor PBMC with patient CD4+T cells[.]" In other words, the specification teaches that the autologous, non-recombinant human immunodefiency viruses are isolated from CD4+ T-cells. Importantly, these CD4+ T-cells are themselves isolated from blood tissues, not cerebrospinal fluid (CSF). The Applicants have amended paragraph [0064] of the specification as described above to include the material incorporated by reference. A Declaration under 37 CFR § 1.68 stating that the amendatory material consists of the same material incorporated by reference in the referencing application is enclosed.

Claims 43 and 46 stand rejected under 35 U.S.C. § 102 as being anticipated by Belardelli. The Applicants respectfully submit that the rejection is now moot in view of the cancellation of those claims.

Claim 44 stands rejected under 35 U.S.C. § 103 as being obvious over Belardelli. The Applicants note that the rejection relies on establishing a *prima facie* case of obviousness, not an alternative rationale to support the conclusion of obviousness. The Applicants also note with appreciation the Examiner's detailed comments hypothetically applying Belardelli to claim 44. The Applicants nonetheless respectfully submit that Belardelli fails to provide disclosure that would render claim 44 obvious. Reasons are set forth below.

First, Belardelli does not teach all the elements of claims 44 and 52-56. Claim 44 recites that the claimed pharmaceutical composition comprises "an antigen presenting dendritic cell comprising antigens from an autologous, inactivated, non-recombinant human immunodeficiency virus (HIV) isolated from blood tissue[.]" Claims 52-56 are dependent on claim 44. Belardelli teaches at paragraph [0164] that the dendritic cells described therein received "HIV-1 SF162 strain [which] was inactivated by AT-2." Cheng-Mayer et al. (86 PNAS 8575 (November 1989) (hereinafter "Chen-Mayer")) describes the isolation and phenotypic characterization of the HIV-1 SF162 virus from an unknown patient over 18 years ago. Importantly, Cheng-Mayer teaches that the HIV-1 SF162 virus used in Beladelli is not an autologous HIV virus isolated from the blood tissue of the individual patient to be treated with the dendritic cells, but instead is a non-autologous virus isolated from blood free, cerebrospinal fluid (CSF). Consequently, Belardelli, does not teach all the elements of amended claims 44 and 52-56 and one of ordinary skill in the art would be unable to use the teachings of Belardelli to achieve the claimed subject matter. Stated differently, the rejection fails to establish the third element of *prima facie* obviousness which requires that the cited prior art reference, or references, teach all the elements of the claimed subject matter.

Second, the Applicants agree with the Examiner's frank acknowledgment that it was not readily apparent from the disclosure in Belardelli that the virus used is non-autologous. The rejection, however, states that it would have been *prima facie* obvious for one skilled in the art to use autologous HIV. In particular, the rejection specifically states:

> However, due to the many variability in the many type of HIV isolates and the ability of the virus to mutate, it would have been prima facie obvious for one of ordinary skill in the art, at the time the invention was made, to use autogolous HIV. One of ordinary skill in the art, at the time the invention was made, would have been motivated to do so to induce immune response against the specific HIV isolate infecting the subject. One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation of success for doing so because the use of autogolous antigens is routinely practiced in the art.

The Applicants respectfully submit that this portion of the rejection is mere speculation that is not supported by any fact on the record. There are a number of ways that this speculative statement manifests itself. Several of those ways are highlighted below.

The Applicants first note that Belardelli relates to the study of properties of (IFN). That is different from the Applicants' objective to provide a composition for treating immunodeficiency viruses. This alone is completely different.

Belardelli itself admits that culturing dendritic cells with GM-CSF and IL-4 is inadequate. This can be seen by reference to Page 2, Paragraph [0020] and Paragraph [0021]. A portion of the relevant text is reproduced below for the Examiner's convenience:

> DCs produced according to this procedure, however, display features of and behave as immature DCs expressing low levels of CD80 and CD86. Consequently, these DCs act as weak stimulators of a specific T cell response and MLR. In this setting, further DC maturation can be driven by the addition of TNFα, IL-1, LPS, monocyte-conditioned medium (22) or sCD40L for two additional days (2, 3).

> Thus, the requirement of a further step for DC maturation by addition of other factors to immature DCs represents a strong limitation for the rapid generation of DCs highly effective for clinical purposes.

In summary, the teaching by Belardelli is that culturing with GM-CSF and IL-4 is not good enough. At best, this results in immature dendritic cells which require <u>further</u> treatment for proper dendritic cell maturation. The Applicants respectfully submit that this admission is hardly suggestive to those skilled in the art to employ this technique. Instead, Belardelli employs further treatment to achieve his goals. This is succinctly stated in Belardelli on Page 2 in Paragraph [0024] which states:

> ...partially mature DCs are obtainable thereby from freshly isolated monocytes after a single step treatment including type I IFN as an essential factor.

In other words, other treatments are effective in the Belardelli protocol because Belardelli realizes that culturing with GM-CSF and IL-4 is quite weak and only results in immature dendritic cells.

Another problem with Belardelli is that there is no discussion of a therapeutic vaccine and, as a consequence, the origin of the virus or the dendritic cell is not considered. Thus, Belardelli provides no teachings which would be of use to one skilled in the art to select autologous or heterologous cells or viruses. As a consequence, the Applicants respectfully submit that the Applicants' claimed use of GM-CSF and IL-4 would hardly be obvious inasmuch as Belardelli actually leads those skilled in the art away from such a treatment.

Yet another problem is that many therapeutic vaccines are developed that are not autologous. Thus, there is plenty of opportunity for those skilled in the art to pursue other means. This is particularly compelling in view of the above statements wherein the Applicants' claimed culturing with GM-CSF and IL-4 is deemed by Belardelli to be inadequate.

However, the Applicants provide further evidence of non-obviousness. In that regard, the Applicants enclose a Declaration of Professor Marie-Lise Gougeon who is well known in the field of HIV/AIDS treatment. Professor Gougeon does not believe that it would have been *prima facie* obvious to use autologous HIV and does not believe that one skilled in the art would have been motivated to do so based on the Belardelli disclosure which admits to the inefficiencies of the GM-CSF and IL-4 culturing methodology. Therefore, Professor Gougeon does not believe that one skilled in the art would have had a reasonable expectation of success. Obviousness rejections cannot be maintained in the absence of a reasonable expectation of success. Withdrawal of the rejection is respectfully requested.

Claims 52-56 stand rejected under 35 U.S.C. §103 over the combination of Lu with Belardelli. The Applicants respectfully submit that Lu does not provide teachings that would cure the deficiencies set forth above with respect to Belardelli. Accordingly, even if one skilled in the art made the hypothetical combination, the compositions would still not result in the subject matter of claims 52-56. Withdrawal of the rejection is respectfully requested.

Claims 43-44, 46 and 52-56 stand provisionally rejected based on obviousness-type double patenting over claims 2, 7 and 13 of co-pending Application No. 11/243,094. Inasmuch as this is a provisional rejection, the Applicants respectfully request that further treatment of this rejection be held in abeyance pending withdrawal of the other rejections.

In light of the foregoing, the Applicants respectfully submit that the entire Application is now in condition for allowance, which is respectfully requested.

Respectfully submitted,

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